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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,273	12/13/1999	JORJ TERRY ULRICH	9950-0002	5731

7590 02/26/2003

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	18

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,273	ULRICH ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-8 and 15-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-8 and 15-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-2, 6-8 and 15-23 are pending.

2. In view of the amendment filed 12/3/02, the following rejections remain.

3. The declaration of Dereck Richardson under 37 C.F.R. § 1.132 filed on 12/3/02 has been fully considered but are not found persuasive because (1) Dereck Richardson states on record that the variety of adjuvant such as aluminum, naturally occurring amino acid such as L-tyrosine are known to enhance general immune response and has been widely used as adjuvant against bacterial and viral infection, which is a Th1 immune response (See page 3 part 9 of the declaration). (2) The declaration of Dereck Richardson further states that DMPL tends to enhance Th1 activity (see page 3, part 11). (3) the data such as the IgG profiles from patient with immunotherapy (Figure 1), the allergen specific IgE profile (Fig 2) as well as skin prick test (Fig 4) from the brochure (appendix A) of allergy therapeutics that describes a vaccine containing allergroid such as rye, birch, tyrosine and 3-DMPL as adjuvant are not significantly different from the placebo control (see overlapping SD).

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 6-8 and 15-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* pharmaceutical composition capable of selectively enhancing a TH1 response over a TH2 response comprising tyrosine, *any* allergen or *any* allergen extract, and 3-DMPL, (2) *any* composition capable of selectively enhancing a TH1 response over a TH2 response comprising tyrosine, *any* allergen or *any* allergen extract, and 3-DMPL wherein the allergen or allergen extract is coated with and/or absorbed onto tyrosine, (3) *any* composition capable of selectively

enhancing a TH1 response over a TH2 response comprising tyrosine, *any* allergen or *any* allergen extract, and 3-DMPL wherein the allergen or allergen extract is coated with the tyrosine, (4) *any* composition mentioned above wherein the allergen or allergen extract is modified by reaction with any cross-linking agent, any cross-linking agent such as dialdehyde or glutaraldehyde, and (5) *any* composition mentioned above wherein the allergen or allergen extract is not modified with any cross-linking agent for treating allergy.

The specification discloses only one modified allergen, that is, glutaraldehyde modified grass pollen extract, and one unmodified ovalbumin coated or absorbed with tyrosine (See page 4 of the specification). The specification defines the term "allergen" includes peptides containing one or more epitopes of any allergen such as allergen fragments, prepared by total synthesis, by enzymatic degradation, or by other means (see page 2 at lines 12-14, in particular).

Other than the specific glutaraldehyde modified grass pollen extract and the unmodified ovalbumin, there is inadequate written description about the structure of any allergen such as those peptides containing one or more epitopes of any allergen such as allergen fragments, prepared by total synthesis, by enzymatic degradation, or by other means. Further, the specification discloses only one modified grass pollen allergen and one unmodified ovalbumin allergen. Given the lack of an additional species of "allergen" or "allergen extract" for a pharmaceutical composition capable of selectively enhanced a TH1 over TH2 response, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 12/3/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the term "optionally" has been deleted from the claims. (2) the specification provides many exemplary species of allergens such as claim 19 recites seven distinct sources from which the allergen or allergen extract may be derived from such as pollen from ragweed or birch, food, insect venom, mould, animal fur, or house dust mite of species of D. farinae or D. pteryssinus.

However, the claims encompass an indefinite number of allergen and allergen extract including peptides containing one or more epitopes of any allergen such as allergen fragments, prepared by total synthesis, by enzymatic degradation, or by other means (see page 2 at lines 12-14, in particular). Further, there are numerous species within the genus of allergen such as ragweed or birch, food, insect venom, mould, animal fur, or house dust mite. The mere mentioned of the genus does not adequately describe and anticipates the undisclosed species within the genus, much less about the fragment containing one or more epitopes of any allergen. Finally, The specification discloses only one modified allergen, that is, glutaraldehyde modified grass pollen extract, and one unmodified ovalbumin coated or absorbed with tyrosine (See page 4 of the specification). Given the lack of an additional species of "allergen" or "allergen extract" for a pharmaceutical composition capable of selectively enhanced a TH1 over TH2 response, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-2, 6-8, 15-17, and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/34626 (PTO 1449) in view of WO 92/16556 (PTO 1449) and US Pat No. 5,795,862 (Aug 1998, PTO 892).

The WO 96/34626 publication teaches a pharmaceutical composition comprising tyrosine and a modified allergen or allergen extract such as glutaraldehyde treated (polymerized) ragweed, birch pollen, food, insect venom, mould, or house dust mite derived from *D fariae or D. pteronyssinus* with physiologically acceptable carrier (See Abstract, page 1, lines 19-22, page 3, line 4-5, in particular). The reference allergen is coated or absorbed onto the reference allergen (See page 3, lines 14-15, claim 2 of WO 96/34626 publication, in particular). The WO 96/34626 publication teaches the reference pharmaceutical composition is useful for desensitization therapy of allergy sufferers (See claims 1-2, and 6-7 of the WO 96/34626 publication, in particular).

The claimed invention differs from the reference only by the recitation that the pharmaceutical composition comprises a 3-DMPL that capable of selectively enhancing TH_1 over TH_2 response and the allergen or allergen extract is not modified.

The WO 92/16556 publication (Van Wijnendale et al) teaches a pharmaceutical composition comprising 3-DMPL, which is an adjuvant for stimulating antigen specific neutralizing antibody and cell mediated immunity (Delayed type hypersensitivity, DTH) by injection (See page 22, example 2a, pages 24-25, pages 28-29 claim 9 of WO 92/16556, in particular) and an antigen such as gp160, which is unmodified. The WO 92/16556 publication further teaches that the adjuvant formulations containing 3D MPL are able to induce a specific T cell response and improve humoral and effector cell mediated (DTH) immune response wherein the DTH immune response is a TH1 response (See page 29, lines 8-16, in particular).

The '862 patent teaches a therapeutic composition comprising un modified allergen such as isolated flea saliva protein and an adjuvant such as Ribi adjuvant from Ribi ImmunoCHem which is 3-DMPL that enhances the immune response to any antigen (See column 42, line 20-35, claims 22 and 24 of '862, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to combine the 3-DMPL adjuvant as taught by the WO 92/16556 publication in a pharmaceutical composition comprising adjuvant such as tyrosine and modified allergen for desensitization therapy as taught by the WO/9634626 publication or substitute the unmodified allergen as taught by the '862 patent for the modified allergen as taught by the WO 96/34626 publication for a pharmaceutical composition comprising tyrosine, allergen or allergen extract, optionally modified with a crosslinking agent and 3-DMPL as taught by the WO 96/34626 publication, WO 92/16556 publication and the '862 patent. From the combined teachings of the

references at the time the invention was made, one would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 92/16556 publication teaches that the adjuvant formulations containing 3D MPL are able to induce a specific T cell response and improve humoral and effector cell mediated (DTH) immune response where DTH is a TH_1 response (See page 29, lines 8-16, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized allergen is useful for desensitization therapy of allergy sufferers since glutaraldehyde modified allergen reduces the antigenicity of said allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular). The '862 patent teaches unmodified allergen and adjuvant such as Ribi adjuvant, which is 3-D MPL is useful in desensitization therapy because it enhances the host immune response to any allergen (See claims 22 and 25 of '862 patent, column 4, lines 19-21 and 30-33, sentence spanning from column 7 bridging column 8, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). Claim 16 is included in this rejection because glutaraldehyde is a species of dialdehyde. The recitation of unmodified allergen or allergen extract is an obvious variation of the teachings of the WO 96/34626 publication because all initial crosslinked (modified) allergen or allergen extract are all start out with unmodified allergen or allergen abstract. The recitation of selectively enhancing a TH1 response over a TH2 response in claim 1 has no patentable weight because it is an inherent property of the reference 3-DMPL adjuvant.

Applicants' arguments filed 12/3/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 1 has been amended to recite the inventive composition selectively enhances a TH1 over a TH2 response. (2) the Examiner has failed to take into account of that the inventive composition selectively enhances a TH1 over a TH2 response. (3) Frank et al do not disclose 3-DMPL and is not relevant to the invention as claimed. (4) the goal of allergy treatment is not merely to enhance TH1 response but to switch the

abnormal T cell response of an allergic patient from a predominantly TH2 driven response to a more pronounced TH1 profile. Neither WO92/16556 nor Frank suggests the formulation containing 3-DMPL would be able to switch the unbalanced predominantly TH2 driven response of an allergic individual to a more pronounced TH1 profile. (4) the inventive formulation enhances much higher levels of IgG2 antibody responses about three orders magnitude than other formulations and does not significantly enhance the IgE response. (5) absence knowledge of the present invention, one of ordinary skill in the art would have expected that both TH1 and TH2 response would be enhanced. (6) In further support of the nonobvious nature of the invention as claimed, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 from Derek Richardson, according to Graham v John Deere, 383 US 1, 148 USPQ 459 (1966), commercial success may present indicia of nonobviousness.

In response to applicant's arguments that the inventive composition enhances a TH1 over a TH2 immune response, it is well-known at the time the invention was made that vaccine formulations containing De-O-acylated monophosphoryl lipid A (3-DMPL) is capable of enhancing cell mediated (DTH) immune response which is a TH_1 response as taught by the WO 92/16556 publication (See page 29, lines 8-16, in particular). It is also well-known at the time the invention was made that tyrosine has been used as adjuvant to coated or to absorbed allergoid such as allergen modified by glutaraldehyde for a pharmaceutical composition for treating allergy as taught by the WO 96/34626 publication. What is not obvious as applicants point out is that the magnitude of IgG1 response compared to other formulation and this is not recite in the claims.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., less allergen specific IgE and three orders of magnitude higher IgG1 levels) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that Frank et al does not disclose 3-DMPL and is not relevant to the invention as claimed, the WO 92/16556 publication (Van Wijnendale et al) teaches a pharmaceutical composition comprising 3-DMPL, which is an adjuvant for stimulating antigen specific neutralizing antibody and cell mediated immunity (Delayed type hypersensitivity, DTH) by injection (See page 22, example 2a, pages 24-25, pages 28-29 claim 9 of WO 92/16556, in particular) and an antigen such as gp160. The WO 92/16556 publication further teaches that the

adjuvant formulations containing 3D MPL are able to induce a specific T cell response and improve humoral and effector cell mediated (DTH) immune response wherein the DTH immune response is a TH1 response (See page 29, lines 8-16, in particular). Further, claim 1 recites a pharmaceutical composition comprising 3-DMPL as one of the ingredients.

In response to applicant's argument the nonobvious nature of the invention as claimed, the declaration of Dereck Richardson under 37 C.F.R. § 1.132 filed on 12/3/02 has been fully considered but are not found persuasive because (1) Dereck Richardson states on record that the variety of adjuvant such as aluminum, naturally occurring amino acid such as L-tyrosine are known to enhance general immune response and has been widely used as adjuvant against bacterial and viral infection, which is a Th1 immune response (See page 3 part 9 of the declaration). (2) The declaration of Dereck Richardson further states that DMPL tends to enhance Th1 activity (see page 3, part 11). (3) the data such as the IgG profiles from patient with immunotherapy (Figure 1), the allergen specific IgE profile (Fig 2) as well as skin prick test (Fig 4) from the brochure (appendix A) of allergy therapeutics that describes a vaccine containing allergroid such as rye, birch, tyrosine and 3-DMPL as adjuvant are not significantly different from the placebo control (see overlapping SD).

9. The following new ground of rejection is necessitated by the amendment filed 12/3/02.

10. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/34626 (PTO 1449) in view of WO 92/16556 (PTO 1449) and US Pat No. 5,795,862 (Aug 1998, PTO 892) as applied to claims 1-2, 6-8, and 15-17 and 19-23 mentioned above and further in view of Marsh et al (PTO 1449), WO 92/16556 (PTO 1449), US Pat No 5,750,110 (May 1998; PTO 892) and Hoyne *et al* (Immunology and Cell Biology 74: 180-186, 1996; PTO 892).

The teachings of the WO 96/34626 publication, the WO 92/16556 publication and the '862 patent have been discussed supra.

The claimed invention in claim 18 differs from the teachings of the references only by the recitation that the composition wherein the allergen or allergen extracts is not modified by reaction with a crosslinking agent.

Marsh *et al* teach unmodified native allergen such as pollen allergen and chemically modified such as formalinized allergen (See page 202, Antigenicity and Allergenicity, second paragraph from the bottom, in particular).

The '110 patent teaches various vaccine compositions comprising 3De-acylated monophosphoryla lipid A (3-DMPL), also known as GB2220 211 (See column 1, lines 11-14, in particular) and HSV-2 gD (See column 4, line 35, in particular) and 3-DMPL, HSV-2 gD and QS21 which is another adjuvant (See abstract, in particular). The '110 patent teaches that a combination of adjuvant such as 3D-MPL and QS21 synergy the production of CTL and gamma interferon response more than twice the sum of individual response while each adjuvant on its own induces cells capable of secreting IFNγ in response to antigen rgD2t (See column 5, lines 16-22, in particular).

Hoyne *et al* teach Th1 cells preferentially secret cytokine such as IFN-γ whereas Th2 cells preferentially secrete IL-4 and IL-10; IFN-γ secreted by Th1 cells can inhibit the growth and differentiation of Th2 cells and vice versa (See page 180, column 1, Introduction, in particular). Hoyne *et al* teach allergen-specific T cells isolated from atoptic patient show an high level of IL-4 and low level of IFN-γ (See page 180, column 1, first paragraph, in particular) and patients who have been desensitized normally display a decrease in Th2 immune response and clinical improvement correlates with a rise in IgG1 and IgG4 levels as well as a decrease in allergen specific IgE (See page 183, column 1, last paragraph, in particular). Hoyne *et al* further teach that a major key to successful immunotherapy may depend on reprogramming the immune response toward TH1 because decreasing the functional response of Th2 cells can lead to improved clinical symptoms such as co-administering allergen in the presence of IFN-γ (See page 183, column 2, first paragraph, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to combine the 3-DMPL adjuvant as taught by the 110 patent or the WO 92/16556 publication or the adjuvant as taught by the '862 patent in a pharmaceutical composition comprising tyrosine, modified allergen or allergen extract coated with tyrosine as taught by the WO 96/34626 publication or unmodified allergen or allergen as taught by Marsh *et al* for a pharmaceutical composition capable of selectively enhancing a TH1 response over a TH2 response as taught by Hoyne *et al* and the'110 patent. From the combined teachings of the references at the time the invention was made, one would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Hoyne *et al* teach that a major key to successful immunotherapy may depend on reprogramming the immune response toward TH1 because decreasing the

functional response of Th2 cells can lead to improved clinical symptoms (See page 183, column 2, first paragraph, in particular). The WO 92/16556 publication teaches that the adjuvant formulations containing 3D MPL are able to induce a specific T cell response and improve humoral and effector cell mediated (DTH) immune response wherein the DTH immune response is a TH1 response (See page 29, lines 8-16, in particular). The '110 patent teaches that the combination of adjuvant such as 3D-MPL and QS21 synergy the production of CTL and gamma interferon response more than twice the sum of individual response while each adjuvant on its own induces cells capable of secreting IFNγ in response to any antigen (See column 5, lines 16-22, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized allergen is useful for desensitization therapy of allergy sufferers since glutaraldehyde modified allergen reduces the antigenicity of said allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

11. Claims 1 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/34626 (PTO 1449) in view of Holen *et al* (Clin Exp Allergy 26(9):1080-8, Sept 1996; PTO 892), WO 92/16556 (PTO 1449), US Pat No 5,750,110 (May 1998; PTO 892) and Hoyne *et al* (Immunology and Cell Biology 74: 180-186, 1996; PTO 892).

The teachings of the WO 96/34626 publication have been discussed supra.

The claimed invention in claim 23 differs from the teachings of the references only by the recitation that the composition wherein the allergen or allergen extracts is ovalbumen.

Holen *et al* teach food allergen such as ovalbumin epitope 105-122 and Human T cells recognizing ovomucoid, lysozyme and ovalbumin (OA) epitope 105-122; Ovomucoid and ovalbumin induced IgE synthesis by a small fraction of B cells (1%) present in the ovalbumin and ovomucoid specific T cell lines (See abstract, in particular). Holen *et al* further teach that OA peptides 105-122 and 323-339 have no affinity to the specific IgE of the two patients, which could be of particular interest regarding the mechanisms of peptide-based immunotherapy.

The WO 92/16556 publication (Van Wijnendale et al) teaches a pharmaceutical composition comprising 3-DMPL, which is an adjuvant for stimulating antigen specific neutralizing antibody and cell mediated immunity (Delayed type hypersensitivity, DTH) by injection (See page 22, example 2a, pages 24-25, pages 28-29 claim 9 of WO 92/16556, in particular) and an antigen such as gp160. The WO 92/16556 publication further teaches that the

adjuvant formulations containing 3D MPL are able to induce a specific T cell response and improve humoral and effector cell mediated (DTH) immune response wherein the DTH immune response is a TH1 response (See page 29, lines 8-16, in particular).

The '110 patent teaches various vaccine compositions comprising 3De-acylated monophosphoryla lipid A (3-DMPL), also known as GB2220 211 (See column 1, lines 11-14, in particular) and HSV-2 gD (See column 4, line 35, in particular) and 3-DMPL, HSV-2 gD and QS21 which is another adjuvant (See abstract, in particular). The '110 patent teaches that a combination of adjuvant such as 3D-MPL and QS21 synergy the production of CTL and gamma interferon response more than twice the sum of individual response while each adjuvant on its own induces cells capable of secreting IFNγ in response to antigen rgD2t (See column 5, lines 16-22, in particular).

Hoyne *et al* teach Th1 cells preferentially secret cytokine such as IFN-γ whereas Th2 cells preferentially secrete IL-4 and IL-10; IFN-γ secreted by Th1 cells can inhibit the growth and differentiation of Th2 cells and vice versa (See page 180, column 1, Introduction, in particular). Hoyne *et al* teach allergen-specific T cells isolated from atoptic patient show an high level of IL-4 and low level of IFN-γ (See page 180, column 1, first paragraph, in particular) and patients who have been desensitized normally display a decrease in Th2 immune response and clinical improvement correlates with a rise in IgG1 and IgG4 levels as well as a decrease in allergen specific IgE (See page 183, column 1, last paragraph, in particular). Hoyne *et al* further teach that a major key to successful immunotherapy may depend on reprogramming the immune response toward TH1 because decreasing the functional response of Th2 cells can lead to improved clinical symptoms such as co-administering allergen in the presence of IFN-γ (See page 183, column 2, first paragraph, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the allergen or allergen extract as taught by the WO 96/34626 publication for the ovalbumin as taught by the Holen *et al* for a pharmaceutical composition comprising tyrosine, ovalbumin and 3-DMPL that is capable of enhancing a Th1 response over a TH2 response as taught by the WO 92/16556 publication, the '110 patent and Hoyne *et al.* From the combined teachings of the references at the time the invention was made, one would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Holen *et al* teach that OA peptides 105-122 and 323-339 have no

affinity to the specific IgE of the two patients which could be of particular interest regarding the mechanisms of peptide-based immunotherapy. The WO 92/16556 publication further teaches that the adjuvant formulations containing 3D MPL are able to induce a specific T cell response and improve humoral and effector cell mediated (DTH) immune response wherein the DTH immune response is a TH1 response (See page 29, lines 8-16, in particular). Hoyne *et al* teach that a major key to successful immunotherapy may depend on reprogramming the immune response toward TH1 because decreasing the functional response of Th2 cells can lead to improved clinical symptoms (See page 183, column 2, first paragraph, in particular). The '110 patent teaches that a combination of adjuvant such as 3D-MPL and QS21 synergy the production of CTL and gamma interferon response more than twice the sum of individual response while each adjuvant on its own induces cells capable of secreting IFNγ in response to any antigen (See column 5, lines 16-22, in particular). The WO/9634626 publication teaches a pharmaceutical composition comprising tyrosine and modified allergen such as glutaraldehyde polymerized allergen is useful for desensitization therapy of allergy sufferers since glutaraldehyde modified allergen reduces the antigenicity of said allergen and tyrosine coprecipitated with the modified allergen (See entire document, page 1, lines 6-10, page 1, line 17-18 and claims of WO96/34626, in particular).

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
February 24, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600